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Published in:
Clinical and Experimental Immunology

DOI:
[10.1111/cei.13125](https://doi.org/10.1111/cei.13125)

Publication date:
2018

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

Shillitoe, B., Bangs, C., Guzman, D., Gennery, A. R., Longhurst, H. J., Slatter, M., Edgar, D. M., Thomas, M., Worth, A., Huissoon, A., Arkwright, P. D., Jolles, S., Bourne, H., Alachkar, H., Savic, S., Kumararatne, D. S., Patel, S., Baxendale, H., Noorani, S., ... Buckland, M. (2018). The United Kingdom Primary Immune Deficiency (UKPID) registry 2012 to 2017. *Clinical and Experimental Immunology*, 192(3), 284-291.
<https://doi.org/10.1111/cei.13125>

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The United Kingdom Primary Immune Deficiency (UKPID) Registry 2012 to 2017

Authors

Ben Shillitoe^{1,2,3}, Catherine Bangs^{1,4}, David Guzman^{1,5}, Andrew R Gennery^{1,2,3}, Hilary J Longhurst⁶, Mary Slatter^{2,3}, David M. Edgar⁷, Moira Thomas⁸, Austen Worth^{1,9}, Aarnoud Huissoon¹⁰, Peter D. Arkwright⁴, Stephen Jolles¹¹, Helen Bourne¹², Hana Alachkar¹³, Sinisa Savic¹⁴, Dinakantha S Kumararatne⁶, Smita Patel¹⁵, Helen Baxendale¹⁶, Sadia Noorani¹⁷, Patrick FK Yong¹⁸, Catherine Waruiru¹⁹, Vijayadurai Pavaladurai²⁰, Peter Kelleher²¹, Richard Herriot²², Jolanta Bernatoniene²³, Malini Bhole²⁴, Cathal Steele²⁵, Grant Hayman²⁶, Alex Richter²⁷, Mark Gompels²⁸, Charu Chopra²⁹, Tomaz Garcez⁴, Matthew Buckland^{1,5,9}

Address of Correspondence

Dr Matthew Buckland

Royal Free and Great Ormond Street Hospitals UCL Centre for Immunodeficiency

Tel +44(0)207 7940500 x34906

Fax +44(0)207 743 1943

mbuckland@nhs.net

Institutes

1. On behalf of the UKPIN Registry Committee, UKPIN
2. Great North Children's Hospital, Newcastle
3. Institute of Cellular Medicine, Newcastle University
4. Manchester University NHS Foundation Trust, Manchester
5. Royal Free Hospital, UCL centre for Immunodeficiency, London
6. Addenbrooke's Hospital, Cambridge Universities NHS Foundation Trust
7. The Royal Hospitals, Belfast
8. NHS Greater Glasgow and Clyde, Glasgow
9. Great Ormond Street Hospital & Institute of Child Health, London
10. Heart of England NHS Foundation Trust, Birmingham
11. University Hospital of Wales, Cardiff
12. The Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle
13. Salford Royal NHS Foundation Trust, Salford
14. Leeds Teaching Hospitals NHS Trust, Leeds
15. John Radcliffe Hospital, Headington, Oxford
16. Papworth NHS Foundation Trust, Cambridge
17. Sandwell and West Birmingham Hospitals NHS Trust, Birmingham
18. Frimley Health NHS Foundation Trust, Frimley
19. Sheffield Children's NHS Foundation Trust, Sheffield
20. Lancashire Teaching Hospitals NHS Foundation Trust
21. Royal Brompton & Harefield NHS Foundation Trust, London
22. NHS Grampian, Aberdeen
23. University Hospitals Bristol NHS Foundation Trust
24. The Dudley Group NHS Foundation Trust, Dudley
25. NHS Tayside, Dundee
26. Epsom & St Helier University Hospitals NHS Trust, St Helier
27. University Hospitals Birmingham NHS Foundation Trust
28. North Bristol NHS Trust, Southmead Hospital, Bristol
29. NHS Lothian, Edinburgh

Key words

Immunodeficiency Diseases, Human, Autoimmunity, Autoinflammatory Disease, Transplantation

Abbreviations

UKPIN	UK Primary Immunodeficiency Network
PID	Primary Immunodeficiency
HSCT	Haematopoietic Stem Cell Transplantation
JAK 3	Janus Kinase 3
ESID	European Society for Immunodeficiencies
CEREDIH	Le Centre de Référence Déficits Immunitaires Héréditaires
CVID	Common Variable Immunodeficiency
HAE	Hereditary Angioedema
IUIS	International Union of Immunological Societies
IQR	Interquartile Range

Summary

This is the second report of the United Kingdom Primary Immunodeficiency (UKPID) registry. The registry will be a decade old in 2018 and, as of August 2017, had recruited 4758 patients encompassing 97% of immunology centres within the UK. This represents a doubling of recruitment into the registry since we reported on 2229 patients included in our first report of 2013. Minimum PID prevalence in the UK is currently 5.90/100,000 and an average incidence of PID between 1980 and 2000 of 7.6 cases per 100,000 UK live births. Data are presented on the frequency of diseases recorded, disease prevalence, diagnostic delay and treatment modality including haematopoietic stem cell transplantation (HSCT) and gene therapy. The registry provides valuable information to clinicians, researchers, service commissioners and industry alike on PID within the UK, which may not otherwise be available without the existence of a well-established registry.

Introduction

Primary immunodeficiencies (PID) are rare diseases with a reported prevalence between 1:16,000 to 1:50,000 (1). The small numbers of patients cared for by individual centres provides challenges to effective diagnosis, clinical care and research. National and international registries have sought to overcome these barriers by encouraging collaboration and providing valuable datasets to clinicians, researchers, pharmaceutical companies and health policy makers. The UKPID registry has provided a unique repository of longitudinal UK data. It was established in 2008 and the first report was published in 2013 covering the first four years of activity (2008-2012) (2). The registry has now expanded to 4758 patients from the 2229 patients in our first report, highlighting the success and efforts of the registry team and local collaborators. Whilst much data overlaps with the ESID registry, establishing a standalone UKPID registry allows the addition of variables that are of importance to UK PID clinicians and researchers that may not otherwise be available from the ESID registry.

Improved recognition of PID and advances in molecular diagnostics have led to a significant increase in the numbers of individual PIDs being recognised with nearly 300 genes identified (3). It is increasingly recognised these PIDs not only present with increased susceptibility to infections, but also immune dysregulation, autoimmunity and an increased susceptibility to malignancy. In addition, an ever-expanding range of treatment options are now available, resulting in improved patient outcomes. Reduced morbidity and mortality following haematopoietic stem cell transplantation (HSCT) means that clinicians are more willing to offer this therapy to a wider range of patients, including adults with PID, and to a greater range of PIDs in a bid for complete cure. Furthermore, new strategies such as gene therapy and newborn screening for severe combined immunodeficiency (SCID), molecular therapy (e.g. JAK inhibitors) and monoclonal antibody therapy are now viable options to include within the UK health care system. Data from national registries provides vital information for clinicians and health policy planners in evaluating the merits of the potential introduction of such strategies.

Methods

The development, ongoing management and technical database structure of the registry was described in our first report (2,4–6). Multicentre Research Ethics (MREC) approval was obtained in 2004 for the ESID online database (MREC number: 04/MRE07/68). Approvals have been amended to reflect the establishment of a UK based database.

A retrospective analysis of the registry data was performed. Minimum prevalence and incidence, as well as live birth data were calculated using UK population data sourced from the Office for National Statistics estimates (7–10). Annual incidence rates have been calculated per 100,000 UK population. Data relating to geographical, gender and sex distribution in addition to age of onset and diagnostic delay were analysed using parametric and non-parametric analysis as appropriate. Where data were only available for a subset of the patients the denominator is stated within the text. The UKPID registry also collects data on patients with secondary antibody deficiency. These patients have been excluded from data pertaining to prevalence and incidence of PID as well as IUIS category breakdown. Their data

has been included to demonstrate their diagnostic delay and immunoglobulin data due to the significant contribution this patient group make to the UK clinical immunology workload and as a comparator cohort for immunoglobulin treated patients with infection.

Data quality continues to be heavily reliant upon qualified users inputting data. Contributing centres are well established within the primary immunodeficiency field. Users must be approved by their head of department and are trained in the documentation of medical data. There is additional ongoing data monitoring by a registry co-ordinator and a nominated person in each centre. The database itself has further features to assure data quality e.g. mandatory fields and logic rules. New entries are reviewed by the registry co-ordinator to ensure no replication has occurred. In addition, the registry is interrogated on a regular basis to detect and correct any further duplicated entries.

Results

There are currently 38 recognised centres in the UK providing specialist immunology services, 37 of which (97%) are actively enrolling patients into the UKPID database, compared to 71% in 2012 (Figure 1). As of August 2017, 4758 patients have been entered into the registry. Recruitment has increased significantly since our 2013 report, which included data on 2229 patients (Figure 2). 4258 patients were alive and being followed up (89.5%). Excluding those patients with secondary antibody deficiency (n=369), this equates to a minimum 2017 UK PID prevalence of 5.90/100,000. 300 (6.3%) patients have died since being entered into the database from the ESID database inception in 2004 and this UKPID registry in 2008. Antibody disorders make up the largest group of patients within the registry with a minimum UK prevalence of 3.92/100,000 (n = 2589, 60%). Prevalence data for the nine IUIS classification categories (3) are shown in Table 1. There were 2399 females and 2359 males registered. 807 (17.0%) patients were 16 years old or less at the time of the latest data entry and collection.

Consanguinity was reported in 118 of 4097 cases (2.9%), equal to the proportion in our previous report (2.9%). 968 of 3971 available cases were identified as familial cases (24.4%), as per our previous report of 24.0%. 1035 (21.8%) patients had a proven genetic defect underlying their PID. 5.7% (177) patients with agammaglobulinemia had a defect in *BTK* and one patient had a defect in the Immunoglobulin Heavy Constant Mu (*IGHM*) gene. 75.5% (n=142) patients with severe combined immunodeficiency (SCID) had a proven genetic defect, with common gamma chain being the commonest, accounting for 32.4% (n=46) of cases. A full breakdown of the genetic defects found in the SCID registry patients is shown in Table 2. 66.6% (n=96) of patients with chronic granulomatous disease (CGD) had a proven genetic defect, with mutations in *CYBB* gene encoding the gp91-phox protein accounting for the majority of cases (68.8%, n = 66). Eighteen (2.7%) of the 678 for whom data was available had their genetic defect diagnosed using whole exome sequencing.

Antibody disorders continue to make up the largest group of all registered patients, accounting for 2821 (59.7%) of a total of 4727 registry patients for whom diagnosis was recorded. The most frequently reported PID is CVID, accounting for 1404 patients (29.7%). The second most frequent diagnosis was hereditary angioedema (HAE) (n = 514, 10.9%). Secondary

hypogammaglobulinaemia (n = 409, 8.7%), unclassified antibody deficiencies (n= 310, 6.6%), agammaglobulinaemia (n=209, 4.4%), unclassified immunodeficiencies (n= 191, 4.0%), SCID (n=188, 4.0%) and specific antibody deficiency (n = 165, 3.5%) were the next most frequent reported diagnoses. The minimum UK prevalence for CVID is 1.93/100,000 population, HAE 0.73/100,000, secondary hypogammaglobulinaemia 0.56/100,000, unclassified antibody deficiency 0.43/100,000, agammaglobulinaemia 0.30/100,000 and SCID 0.26/100,000. A full list of prevalence rates for all diseases recorded within the registry can be found in supplementary Table 1.

The median annual prevalence of PID from 2010-2015 was 0.38 new cases per 100,000 UK population (1 per 270270), peaking at 0.44 new cases per 100,000 UK population in 2012 (1 per 227518). The incidence per 100,000 UK live births is shown in Figure 3. There is a clear rise in incidence per 100,000 live UK births from the mid-1980s. This is likely to be due to an increased recognition of PID, resulting in more patients being entered into the registry enabling a truer reflection of incidence. In addition, with modern management, many patients are expected to live into adulthood, thereby increasing the number of cases of inherited PID in addition to any *de novo* genetic mutations. The apparent drop in incidence seen in Figure 3, from 2000 is a result of cases born in this time period not yet diagnosed with PID (e.g. CVID). From 1980 to 2000 the minimum median incidence of PID was 7.60 cases per 100,000 UK live births or 1 per 13157 births.

Diagnostic delay can negatively affect outcome in PID. Prompt diagnosis improves outcomes following HSCT for SCID (11–13) and is recognised as an important prognostic indicator in antibody deficiencies (14–16). The current median diagnostic delay for SCID was 60 days (IQR 0-121). The current median diagnostic delay in CVID was 4 years (IQR 1-10) Spearman's correlation demonstrates a statistically significant but weak correlation for a decreasing diagnostic delay over time for CVID ($r_s = -0.719$, $p = 0.0213$). For agammaglobulinaemia the median delay is 1 year (IQR 0-2). For the 3912 patients for whom data is available, the main presenting symptom is infection related, accounting for 76.8% of patients followed by immune dysregulation with 8.1%. Presenting symptom and diagnostic delay by diagnosis and IUIS category are shown in Table 3.

A total of 2836 patients are recorded to have received immunoglobulin replacement therapy (59.6% of the total 4758 registry patients). 1391 (49%) received this by intravenous route and 1440 (51%) by subcutaneous route. 1669 (58.9%) received their infusion at home. The median dose of immunoglobulin was 514mg/kg/month (IQR 424-645) with a median interval of 3 weeks.

A total of 679 patients were recorded as having received a haematopoietic stem cell transplant (HSCT) since 1973 with the majority (87.2%) transplanted after 2000 (Figure 4). 310 (45.7%) received their HSCT from donor blood marrow, 200 (29.5%) from peripheral blood stem cells, 59 (8.7%) from cord blood stem cells and in 110 (16.2%) the donor was not recorded. 294 (43.3%) were matched unrelated donor (MUD), 167 (24.6%) matched sibling donor (MSD), 77 (11.3%) haploidentical, 73 (10.8%) mismatched unrelated donor (MMUD), 2 (0.3%) autologous and in 66 (9.7%) the source was unrecorded. Autologous HSCT is not a standard of care in PID;

there are no further data on these two cases recorded in this registry. The overall survival rate for HSCT in this registry is 83.8% with a mortality of 7.7% (8.5% are either discharged or lost to follow up). Since 2000, 26 patients have undergone gene therapy. The survival for gene therapy patients in the registry is currently 100%.

Discussion

The UKPID registry celebrates its tenth birthday in 2018. Over this decade almost all immunology centres in the UK have actively contributed to the database and the number of recruited patients continues to grow each year. London and Newcastle (supra-regional centres for transplantation of paediatric PID) continue to provide a large contribution to the database (accounting for 25.0% and 12.6% of the total registry respectively). The wide geographical spread of actively recruiting centres should ensure the registry accurately reflects the pattern of health care service access and delivery across the UK.

The UKPID registry allows easy to access and reliable datasets for clinicians and researchers. This enables assessment of patient outcomes to be done in a timely and effective manner such as that seen in the recent work from Stubbs *et al.* suggesting that patients with agammaglobulinaemia in the UK suffer from deteriorating pulmonary health despite current therapies (17). Compiling such a body of work without the aid of the UKPID registry would result in considerable additional work load and time to the research process.

Since our first report, we estimated the number of patients with PID in the UK to be between 4000 and 5000. Our latest count of 4258 verified, live patients is extremely encouraging. The minimum prevalence of PID in the UK with this latest data stands at 5.90/100,000 population. This is similar to the reported incidence in France of 6.06 per 100,000 and larger than Switzerland (4.16 per 100,000) and Germany (2.11 per 100,000) (1). These disparities are likely to be due to differences in reporting as individual countries continue to develop their own reporting strategies. With the coverage of the UKPID registry (97% of immunology centres), we feel this minimum incidence is an accurate reflection of the burden of PID within the general population. It is possible this is still an underestimate with some patients not recruited to the registry and some patients being treated at hospitals not designated as immunology centres, but these numbers are likely to be small. However, a recent epidemiological field survey from Mahlaoui *et al.* suggests the true minimum prevalence of PID in France is actually 11 per 100,000 population and may therefore mean these numbers still significantly underestimate the true burden of PID within the population (18).

The expansion in registry patients also enables us to calculate a reliable estimate of PID incidence per UK annual live births. The data showed a median PID incidence from 1980-2000 of 1 in 13157 births. This number is still likely to be an underestimate of the true value, with a significant proportion of patients in this period dying either before their PID is recognised or before the establishment of the UKPID registry. With the registry now firmly established, we hope to increase the accuracy of these data for future reports. The proportion of under 16 year olds in the database is currently 17.0%, similar to the under 16 year old proportion of the general UK population at 18.8% (7).

Antibody deficiencies continue to account for the largest group of PID cases within the registry (60%), has remained stable since our first report and is in keeping with other registries.(1)

Clinicians continually strive to diagnose patients earlier to improve patient outcomes. Nearly a quarter of patients presented with symptoms other than recurrent infections. Non-infectious presentations such as autoimmune cytopenias, inflammatory bowel disease and malignancy are increasingly being recognised as possible presentations of PID (19–22). The median diagnostic delay for patients who presented with malignancy is 4 years, the highest amongst the presenting symptoms recorded by our registry. Increased awareness of these facts as demonstrated by these data and those of others should hopefully result in reductions in diagnostic delay for future patients.

Increased awareness of the genetic basis of PID and thus the importance of screening newborn siblings of affected patients will help reduce delays. Newborn screening for SCID by measuring T-cell receptor excision circles (TRECs) on the newborn blood spot is due to start in the UK in 2018 under a pilot programme, which may offer significant improvements in event free survival for SCID patients in the UK. Diagnostic delay in the diagnosis of agammaglobulinaemia remains consistent at one year. Newborn screening for congenital B cell deficiencies is possible using a similar technique to SCID screening, by measuring kappa-deleting recombination excision circles (KRECs) on the newborn blood spot. Some countries do indeed combine a TREC/KREC screening programme but the effectiveness of a KREC screening programme is currently unknown.

Immunoglobulin therapy remains the mainstay of treatment for the vast majority of antibody deficiency syndromes. The proportion of those patients receiving intravenous immunoglobulin therapy (IVIG) has fallen from 60% in our previous report to an equal split in the cohort between intravenous and subcutaneous therapies (SCIG). For the 2836 patients recorded as receiving immunoglobulin therapy over half (59%) receive their therapy at home. This data highlights the patient preference for therapy at home and should continue to be actively offered to all patients wherever possible.

Better understanding of, and access to genetic testing can enable faster and more accurate diagnosis of PID leading to improved outcomes (23). Nearly a quarter of the registry patients have a proven gene defect underlying their PID, although the number of patients who had genetic testing but no defect found is unknown in this registry data. In the previous report (2014) only 20 patients had a recorded genetic diagnosis, significant work to improve capture of genetic diagnoses has been undertaken. Diseases like agammaglobulinaemia continue to show a high proportion of cases where a genetic defect is found (85%). However, common diseases such as CVID continue to show a low proportion of cases for which a genetic defect is found (1.78%). Next generation sequencing looks set to supersede conventional Sanger sequencing in the coming years leading to a potentially higher proportion of patients for whom a genetic defect is known and to the discovery of new PIDs (24).

The UKPID registry is now firmly established within the UK and data is available for the majority of PID patients. This dataset enables a relatively accurate estimate of disease burden

of primary immunodeficiency within the UK. Over the next 5-10 years we hope to continue this successful recruitment as well as adding the next level of registry data encompassing more detailed diagnostic and follow-up data e.g. infection incidence, medication, vaccinations, lung function, laboratory values and quality of life. It is also planned to include further therapeutic data, most notably the use of biologicals and targeted therapy, for which this registry could provide a useful data source for surveying the use of these agents. These extra levels of detail will further enable accurate assessment of outcomes in PID to be done quickly and with relative ease than would otherwise be possible without such a registry. As research in PID advances there is likely to be an increasing range of interventions available to patients. The ability to evaluate current outcomes in a timely manner will be vital to ensuring patients are able to access the best possible care. We look forward to working with researchers and clinicians in providing reliable, detailed data on PID within the UK to aid research, rational resource allocation and improvements in clinical care.

Acknowledgements

D. Mullen (NHS Grampian); L. Lorenzo, J. Dempster, S. Grigoriadou (Barts Health NHS Trust); L. Devlin (Belfast Health and Social Care Trust); C. Jones, M. Kusano (Sandwell and West Birmingham Hospitals); J. Daglish, S. Onyango-Odera, S. Hackett (Heart of England NHS Trust); E. Knight (University Hospitals Birmingham NHS Foundation Trust); F. Manyika (University Hospitals Bristol NHS Foundation Trust); L. Jennings, L. Smith (North Bristol NHS Trust); A. Manson, M. Fordham, A. Chandra, M. Krishna (Cambridge University Hospitals NHS Foundation Trust); K. Henderson, H. Gronlund (Papworth Hospital NHS Foundation Trust); E. Carne, C. Joyce, C. Kingdon, T. El-Shanawany (Cardiff and Vale University Health Board); G. Menzies (NHS Tayside); G. Paul, D. Baxter (NHS Lothian); M. Milarionmayieka (Epsom and St Helier University Hospitals); C. Quinn (Frimley Health NHS Foundation Trust); M. Brownlie, H. Millar, S. Murng (NHS Greater Glasgow and Clyde), R. Savjani (Great Ormond Street Hospital for Children NHS Foundation Trust); J. Moor, B. Fish (Hull and East Yorkshire Hospitals NHS Trust); K. Ford, J. Toolan, P. Wood, G. Arumugakani (The Leeds Teaching Hospitals NHS Trust); J. Berry (The Royal Liverpool and Broadgreen University Hospitals); C. Beeson (Alder Hey Children’s NHS Foundation Trust); B. Boardman, S. Hughes (Manchester University NHS Foundation Trust); T. Green, O. Grix, S. Elcombe, C. Stroud, P. Tierney, A. Cant (The Newcastle upon Tyne Hospitals NHS Foundation Trust); R. Weldon, E. Drewe, P. Madhuri Vaitla (Nottingham University Hospitals NHS Trust); A. Welby, R. Jain (Oxford University Hospitals NHS Foundation Trust); C. Symons, T. Trump, A. Whyte (Plymouth Hospitals NHS Trust); K. Haworth, A. Anantharachagan (Lancashire Teaching Hospitals NHS Foundation Trust); S. Workman, A. Symes (Royal Free London NHS Foundation Trust); L. Common, I. Jones, M. Fernandez, A. Herwadkar (Salford Royal NHS Foundation Trust); A. Ford, F. Shackley (Sheffield Children’s NHS Foundation Trust); F. Ashworth, A. Shrimpton (Sheffield Teaching Hospitals NHS Foundation Trust); S. Fenton-Edwards, W. Rae, E. Eren (University Hospital Southampton NHS Foundation Trust); C. Bowmar-Scothern (St George’s University Hospitals NHS Foundation Trust)

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Conflicts of Interest

Ben Shillitoe, Catherine Bangs, David Guzman, Andrew Gennery, Mary Slatter, Moira Thomas, Aarnoud Huissoon, Peter Arkwright, Hana Alachkar, Sinisa Savic, Smita Patel, Helen Baxendale, Saida Noorani, Patrik Young, Catherine Waruiru, Peter Kelleher, Richard Herriot, Jolanta Bernatonienne, Grant Hayman and Alex Richter have no COIs to declare.

Hilary Longhurst has contributed as a research support, educational support, speaker's bureau, advisor to Biotest, CSL Behring, Shire (Baxalta) and as an advisor to Octapharma.

David Edgar (JDME) has received fees for speaking (Shire Israel), and consulting (Shire UK, Octapharma UK, Grifols UK and CSL Behring UK).

Austen Worth has worked as a paid consultant for Biotest UK, working on an advisory board for the use of CMV specific immunoglobulin.

Stephen Jolles has received support for speaker, congress, advisory boards, clinical trials, DSMB, and projects from CSL Behring, LFB, Shire, Biotest, Grifols, BPL, Octapharma, UCB Pharma, Binding Site, Sanofi, GSK and SOBI.

Helen Bourne acted as paid consultant to Baxter and Biotest and has received reimbursement for symposium attendance by CSL Behring, Baxter, Biotest and Octopharma.

Dinakantha Kumararatne has between 2013 and 2018, been funded to attend scientific meetings by CSL Behring and Shire and Biotest, and been paid for delivery of a lecture by Biotest and acted as a paid consultant to Shire.

Pavaladurai Vijayadurai has received financial support from Binding Site and Shire to attend symposiums.

Malini Bhole has attended the global forum for HAE and ESID 2016 sponsored by Shire, and the Biotest Immunology Forum sponsored by Biotest.

Cathal Steele has received education grants from CLS Behring, Alk and Baxter.

Mark Gompels has received payments from BioCryst pharmaceuticals for advisory board work and Educational grants from Novartis pharmaceuticals, Bristol Myers and has ongoing research trials with Merck and Viiv.

Charu Chopra has received re-imbursement from CSL Behring to attend the large PID Congress (ESID Conference) in 2016 and 2017.

Tomaz Garcez is chair of UKPIN, has received financial support to attend conferences from CSL and Shire contributes to a paid advisory board and chairing work for CSL and Shire

Matthew Buckland has received funding for trips or meetings and/or consultancy from Shire, Octopharma, CSL Behring and Biotest

Figure legends

Figure 1 Geographical distribution of patients enrolled in the UKPID Registry by city or town of documenting centre. The diameter of the circle is directly proportional to the number of patients enrolled in each centre

Figure 2 Recruitment of total patient numbers into the United Kingdom Primary Immunodeficiency Registry

Figure 3 UK Incidence of registered PID per 100,000 live births

Figure 4 Number of PID patients undergoing HSCT or Gene Therapy

For Peer Review

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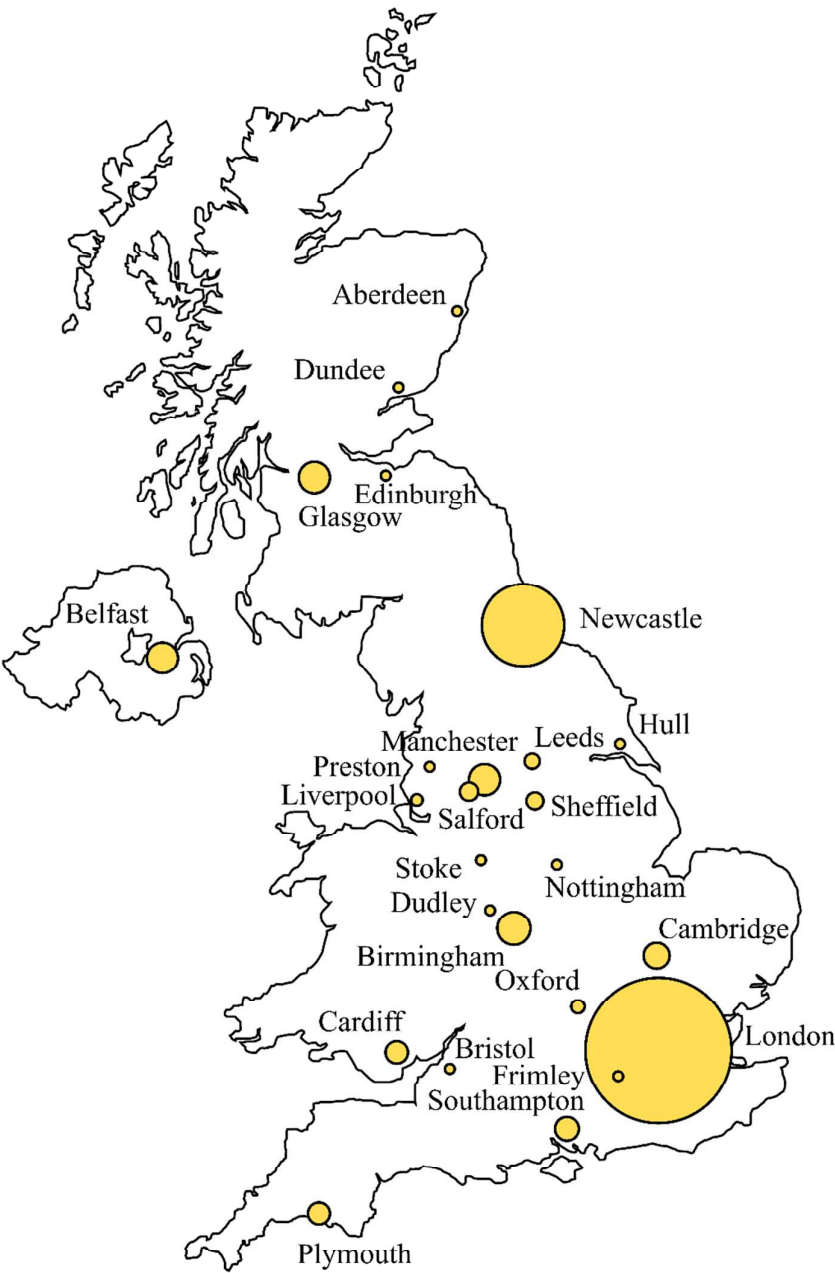


Figure 2 Recruitment of total patient numbers into the United Kingdom Primary Immunodeficiency Registry

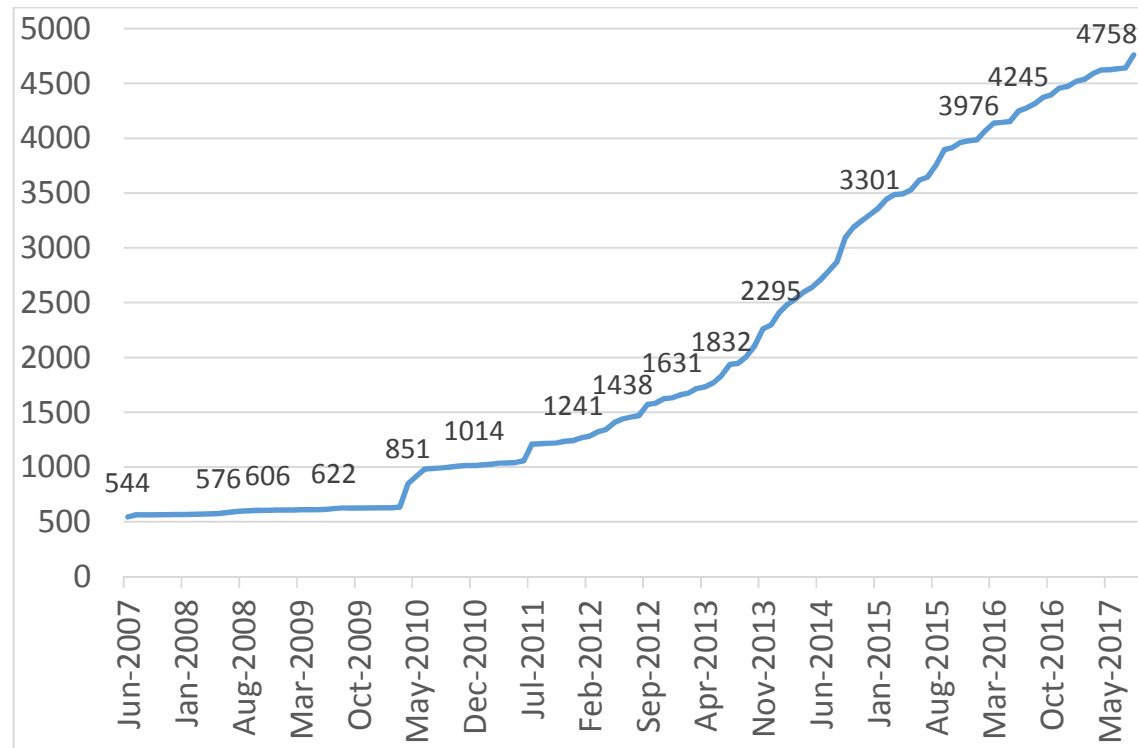


Figure 3 UK Incidence of registered PID per 100,000 live births

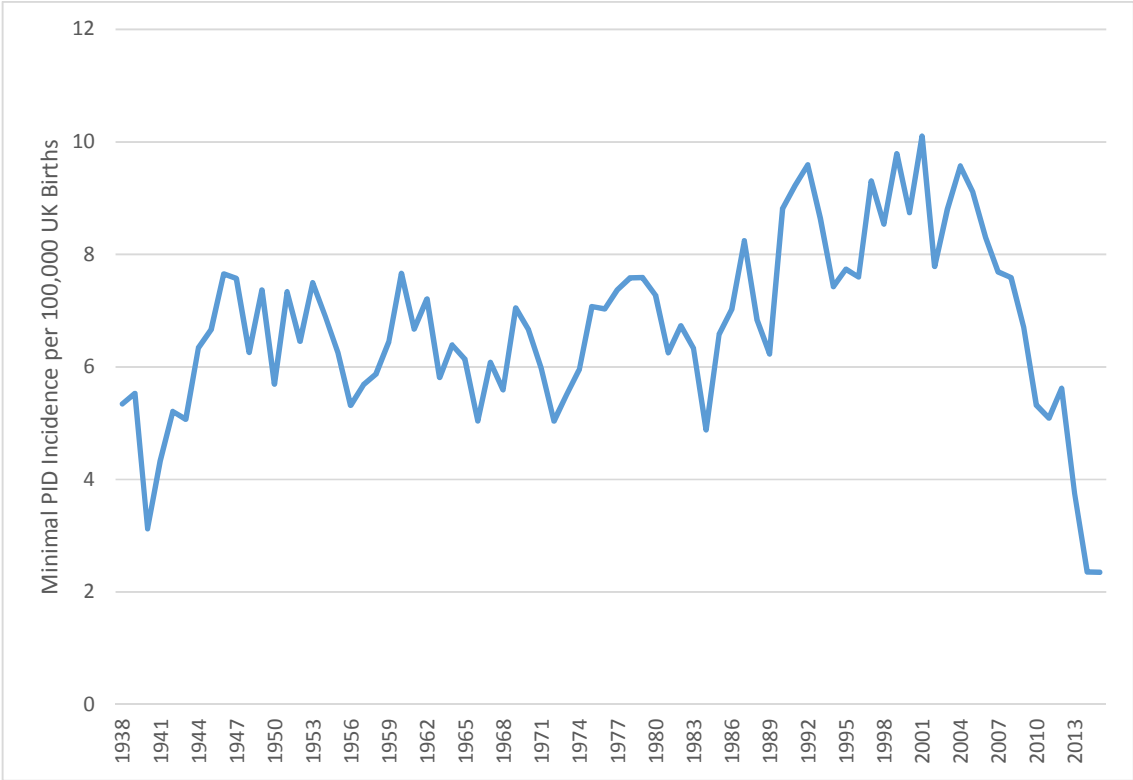


Figure 4 Number of PID patients undergoing HSCT or Gene Therapy

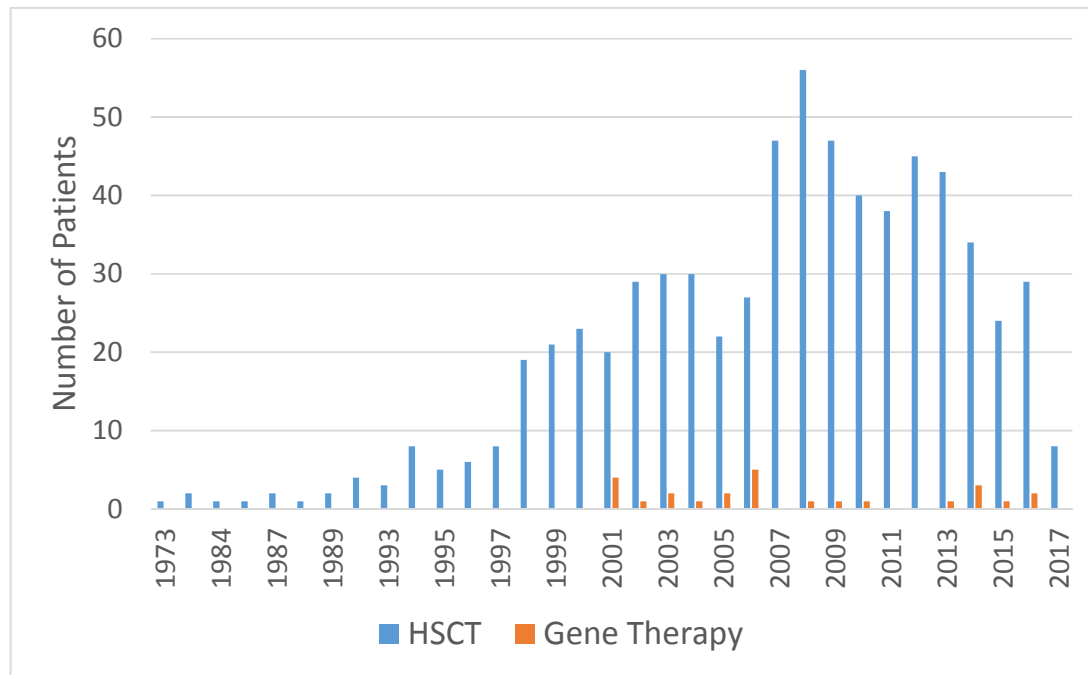


Table 1 Frequency table for International Union of Immunological Sciences (IUIS) classification and minimum disease prevalence. Estimated minimum prevalence data for PID in the United Kingdom is based on a national population of 66,029,990 (Source: Office for National Statistics)

IUIS Classification	n (alive patients)	UK Prevalence/100,000
Auto inflammatory disorders	25	0.04
Combined immunodeficiencies	329	0.50
Complement deficiencies	559	0.85
Defects in innate immunity	39	0.06
Diseases of immune dysregulation	94	0.14
Other well defined PIDs	325	0.49
Phagocytic disorders	177	0.27
Predominantly antibody disorders	2589	3.92
Unclassified Immunodeficiencies	160	0.24

Table 2 Genetic Defects in SCID registry patients

Genetic Defect	Number of Cases	Proportion (%)
Common Gamma Chain (X-linked)	46	32.39
ADA	38	26.76
IL7Ralpha	14	9.86
JAK3	11	7.75
RAG1	15	10.56
Artemis	10	7.04
RAG2	3	2.11
IL21R	3	2.11
CD3e	1	0.70
LIG4	1	0.70

Table 3 Diagnostic Delay and main presenting symptom for the commonest PIDs and IUIS category in years (median, 25th and 75th quartiles)

	Min	25 th quartile	Median	75 th quartile	Max	Immune Dysregulation	Infections	Malignancy	Syndromal	Other
PID										
CVID	0	1	4	10	69	5.1%	93.7%	0.1%	0.1%	1.0%
Hereditary Angioedema	0	0	2	10	55	0.0%	0.3%	0.0%	2.0%	97.7%
Secondary hypogammaglobulinaemia	0	0	1	3	64	1.9%	96.7%	0.8%	0.0%	0.6%
Agammaglobulinemia	0	0	1	2	44	0.0%	98.2%	0.0%	0.6%	1.2%
Unclassified antibody deficiency	0	1	2	5	61	3.0%	93.7%	0.3%	0.3%	2.6%
Age										
< 18 years	0	0	0	1	14	19.2%	65.7%	0.0%	8.7%	6.4%
between 18 and 65	0	1	3	8	48	1.2%	89.6%	0.4%	0.4%	8.4%
> 65 years	0	1	3	10	69	7.0%	76.2%	0.3%	1.6%	14.9%
IUIS Category										
Autoinflammatory disorders	0	2.5	6	10.5	33	81.8%	0.0%	0.0%	9.1%	9.1%
Combined immunodeficiencies	0	0	0	1	47	17.6%	77.9%	0.0%	1.5%	3.1%
Complement deficiencies	0	0	1	8	55	0.0%	10.6%	0.0%	1.9%	87.4%

Defects in innate immunity	0	1	2	6	61	4.8%	88.1%	0.0%	4.8%	2.4%
Diseases of immune dysregulation	0	0	1	4	43	67.0%	26.2%	0.0%	4.9%	1.9%
Other well defined PIDs	0	0	1	3.5	66	19.9%	50.7%	0.0%	27.2%	2.2%
Phagocytic disorders	0	0	1	3	37	14.5%	83.6%	0.0%	1.2%	0.6%
Predominantly antibody disorders	0	1	3	8	69	3.5%	94.3%	0.4%	0.1%	1.6%
Unclassified Immunodeficiencies	0	0	2	9	66	14.8%	80.0%	0.7%	2.2%	2.2%
Presenting Symptom										
Immune dysregulation	0	0	1	6	43					
Infections	0	1	2	6	67					
Malignancy	0	3	4	4.25	5					
Syndromal	0	0	1	8	55					
Other	0	0	0	2.25	11					

Supplementary Table

Supplementary Table 1 Frequency table for individual diagnosis for live patients and disease prevalence. Estimated data for PID in the UK based on national population of 66,029,900 (Source: Office for National Statistics)

	n	Minimum Prevalence/100,000
CVID	1273	1.93
Hereditary Angioedema (HAE)	482	0.73
Secondary hypogammaglobulinaemia	369	0.56
Unclassified antibody deficiency	285	0.43
Agammaglobulinemia	195	0.30
Severe Combined Immunodeficiency (SCID)	170	0.26
Unclassified immunodeficiency	159	0.21
Specific IgG deficiency (SPAD)	139	0.21
Chronic Granulomatous Disease (CGD)	123	0.19
Combined Immunodeficiency	117	0.18
Di George syndrome	99	0.15
IgA deficiency	71	0.11
Thymoma	68	0.10
CSR / HIGM (Hyper-IgM)	68	0.10
Wiskott-Aldrich syndrome	66	0.10
Hyper IgE Syndrome (HIES)	53	0.08
IgG subclass deficiency	44	0.07
Ataxia-Telangiectasia	40	0.06
Autoimmune lymphoproliferative syndrome (ALPS)	29	0.04
Acquired angioedema	22	0.03
Omenn syndrome	22	0.03
Immune dysregulation, unclassified	18	0.03
Congenital neutropenia	18	0.03
Cartilage hair hypoplasia	16	0.02
Mendelian susceptibility to mycobacterial infection	15	0.02
IgA with IgG subclass deficiency	14	0.02
TLR/NFkappa-B	14	0.02

Complement ID, unclassified	14	0.02
Mannan Binding Lectin Deficiency (MBL)	13	0.02
Chronic mucocutaneous candidiasis (CMC)	13	0.02
Activated PI3K-delta syndrome (APDS)	13	0.02
Unclassified autoinflammatory	12	0.02
Transient hypogammaglobulinaemia	12	0.02
Syndromic PID, unclassified	12	0.02
C2 deficiency	11	0.02
Innate ID, unclassified	10	0.02
Leucocyte adhesion deficiency (LAD)	10	0.02
Unclassified phagocytic disorders	9	0.02
Autoimmune polyendocrinopathy candidiasis and ectodermal dystrophy (APECED)	8	0.01
TNF-receptor associated periodic fever syndrome (TRAPS)	8	0.01
CD4 deficiency	7	10.02
HLA class II deficiency	7	0.01
IPEX-like disease	7	0.01
Nijmegen breakage syndrome (NBS1)	7	0.01
X-linked lymphoproliferative syndrome (XLP)	6	0.01
Familial haemophagocytic lymphohistiocytosis syndromes (FHLH)	6	0.01
FOXP3 deficiency (IPEX)	5	0.01
Factor I deficiency	5	0.01
Immunodeficiency with Centromere Instability and Facial Anomalies (ICF)	5	0.01
C7 deficiency	3	<0.01
Factor D deficiency	3	<0.01
Chediak Higashi syndrome	3	<0.01
Early-onset multi-organ AI	3	<0.01
Hyper IgD syndrome (MVK)	3	<0.01
Ivemark syndrome	2	<0.01
AT-like disorder	2	<0.01

C1 deficiency	2	<0.01
C8 deficiency	2	<0.01
Cyclic neutropenia	2	<0.01
Vitamin B12 and Folate metabolism	2	<0.01
CD25 deficiency	2	<0.01
MonoMAC	2	<0.01
Netherton syndrome	2	<0.01
Properdin P factor complement deficiency (PFC)	2	<0.01
IgM deficiency	2	<0.01
Atypical SCID	2	<0.01
CD8 deficiency	2	<0.01
CHARGE syndrome	1	<0.01
C4 deficiency	1	<0.01
Griscelli, type 2	1	<0.01
HLA class I deficiency	1	<0.01
Muckle-Wells syndrome	1	<0.01
Periodic fever aphthous stomatitis, pharyngitis and adenopathy (PFAPA)	1	<0.01
Ras-associated lymphoproliferative disease (RALD)	1	
Severe viral infection	1	<0.01
Reticular Dysgenesis (AK2)	1	<0.01
Shwachman-Diamond-syndrome	1	<0.01
Warts hypogammaglobulinaemia infections and myelokathexis (WHIM)	1	<0.01
XLT (WASP)	1	<0.01